Remarks

Claims 1, 4, 8-11, 31, 35, 42, 43, 49, 55, 59, and 64 are pending in the application. Claims 4 and 31 have been amended to delete references to previously cancelled claims.

§112 Rejections

I. Claims 1, 4, 8-11, 31, 35, 42, 43, 49, 55, 59, and 64 were rejected under USC §112, first paragraph for non-enablement over the scope of the claims.

Examiner has made several statements which are inaccurate which Applicant would like to address.

Firstly, Examiner made the following statement:

> "It should be noted that SR141716A was approved by FDA in 2006, long after applicants had filed their invention. Thus at the time the invention was made the activity was not known."

SR141716A (known as rimonabant or under the tradenames: Acomplia™ in Europe and Zimulti™ in the US) was not approved by the FDA in 2006; however, it was authorized for marketing in Europe on June 19, 2006 as an anti-obesity agent. The fact that SR141716A wasn't approved until 2006 is totally immaterial with respect to the known activity of the compound. Clearly, the activity of a compound is not just miraculously known when it is approved by a regulatory agency. Several years of research and clinical trial data had been completed and reported upon prior to the official approval. Examiner totally ignored the references that were submitted with the IDS forms made of record in the IDS entered on July 29, 2004 and acknowledged by the Examiner on September 14, 2005, including the two references referred to in the previous amendment:

Colombo, G., et al., "***Appetite Suppression and Weight Loss after the Cannabinoid Antagonist SR141716***," Life Sci, 63, PL113-PL117 (***1998***); and

Pertwee, R.G., "Pharmacology of Cannabinoid Receptor Ligands" Curr Med Chem, 6, 635-664 (***1999***). - emphasis added

Both of these articles were in the public domain prior to the time of the present invention and clearly establish that CB-1 antagonists (or inverse agonists) were known to be useful as anti-obesity agents, as well as other indications.

Secondly, Examiner made the following statement which is also incorrect:

> "Secondly the SR141716A has now been taken off the market because of the increased side effects. See the article from Wikepedia attached."

First of all, Wikepedia is not a recognized authority. That being said, Examiner has totally misinterpreted the article. The article clearly states that "Sanofi-Aventis announced that it was withdrawing the new drug application (NDA) for rimonabant and would resubmit an application at some point in the future." Obviously, SR141716A was not approved for marketing in the US; therefore, it could not have been "taken off the market" as asserted by the Examiner. Although the FDA in the US did not approve the marketing of rimonabant in the US, it does not mean that it will not in the future. In fact, Sanofi has stated in the press that they will re-submit their NDA. Just because a drug has side effects does not mean that it is not useful for the intended indication. Most drugs have side effects. The FDA addresses these concerns in various ways including warning labels. In addition, there are several CB-1 antagonists (inverse agonists) currently in clinical trials as anti-obesity agents. (e.g., MK-0364 or L-000899055 (also known as taranabant from Merck) and CP-945598 (also known as otenabant from Pfizer)).

More importantly, SR141716A has not been taken off the market in Europe. See, the following website which is a recognized authority for pharmaceutical medications (European Medicines Agency).

http://www.emea.europa.eu/humandocs/Humans/EPAR/acomplia/acomplia.html

A copy of the EPARs for Acomplia™ is attached hereto for the Examiner's convenience. SR141716A (Acomplia™) is currently being sold in Europe as an anti-obesity agent. Clearly, compounds that act as CB-1 antagonist/inverse agonist have been shown to be successful in the treatment of obesity. Therefore, Examiner rejection based on lack of utility is unfounded.

Thirdly, the Examiner also misinterpreted the reference by Muccioli. The Examiner states the following:

> "Table 4, page 1366, teaches compounds similar to SR141716 with a slight different in the substituent "R" and the activity of the compounds change from ***inverse antagonist*** to neutral antagonist." *Emphasis added*

The function reported in Table 4 of the reference is not an "*inverse antagonist*" as asserted by the Examiner but instead is an "*inverse agonist*". SR141716 is known to act as both a competitive antagonist and inverse agonist at the CB-1 receptor and is often referred to as a CB-1 antagonist/inverse agonist. Therefore, the art is not very unpredictable as asserted by the Examiner. Applicant can rely on the fact that SR141716 was known to act as a CB-1

antagonist/inverse agonist with its associated uses as a reasonable basis for utility of their compounds as tested in similar assays (e.g., competitive antagonist assay). Examiner has provided no credible evidence to the contrary.

Even though Muccioli did not discuss the fact that CB-1 antagonists or inverse agonists are useful as anti-obesity agents, as pointed out above, others have discussed their uses as anti-obesity agents as well as other indications in the literature. See the numerous references cited in the previous IDS forms of record. As stated in MPEP 2107.03,

> "The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. An applicant can establish a reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof.

The MPEP also states that data generated using *in vitro* assays almost invariably will be sufficient to establish therapeutic or pharmacological utility for the compound, composition or process. Applicants respectfully submit that he has provided a reasonable correlation based on the numerous articles submitted in the IDS forms of record and the binding data submitted in the specification. Examiner has failed to provide any credible evidence contradicting this reasonable correlation.

The Examiner repeated the rejection from the previous office action; however, she ignored the amendments to the claims in the previous response to that office action. Applicant would like to point out that the majority of the rejection was directed to subject matter that is no longer part of the claims as previously amended. For example R^0 and R^1 have both been amended to a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1$-$C_4)$alkoxy, halo-substituted $(C_1$-$C_4)$alkyl, and cyano and R^4 was amended to a $(C_1$-$C_8)$alkyl, halo-substituted $(C_1$-$C_8)$alkyl, cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-4-yl. Examiner admitted on the record that the specification is enabling for compounds wherein R^1 and R^0 are aryl(phenyl) with halogen or methoxy substituents, or R^4 is an alkyl, halogen substituted alkyl or a cycloalkyl, which basically represents only those compound exemplified in the specification. However, Examiner is refusing to allow a reasonable genus surrounding the exemplified compounds which is contrary to established law.

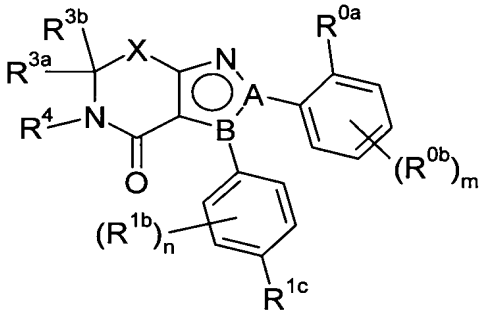
As part of the enablement requirement, it is well-established that one does not have to provide exemplification of every compound that falls within the scope of the claims. Clearly, it is well within the skill of the art to make compounds as presented claimed. Examiner has failed to provide any credible evidence to the contrary. In addition, as discussed above, Examiner has failed to provide any credible evidence to refute Applicant's reasonable correlation of utility for the presently claimed compounds.

Obviousness-Type Double Patenting Rejections

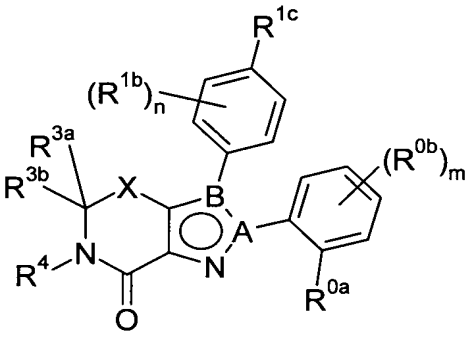
Before addressing the following rejections on the merits, it is important to note that US 7,230,024; US 7,241,788 and US 7,145,012 are all from the same family of patent applications. Both US 7,241,788 and US 7,230,024 are divisionals of US 7,145,012.

II. Claims 1, 4, 8-11, 31, 35, 42, 43, 49, 55, 59, and 64 were rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-23 of US Patent No. 7,230,024.

Examiner recognizes that the cores are not identical but asserts that the cores are similar and are therefore not patentably distinct from each other. Applicant respectfully disagrees. Although the structures appear to be similar, it is important to note that the orientation of the R^0 and R^1 groups are different. (see illustration below where R^0 and R^1 are substituted phenyls).



(III)



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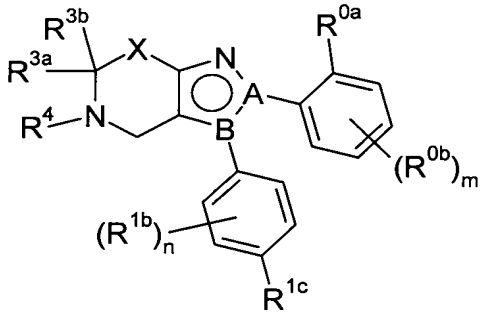
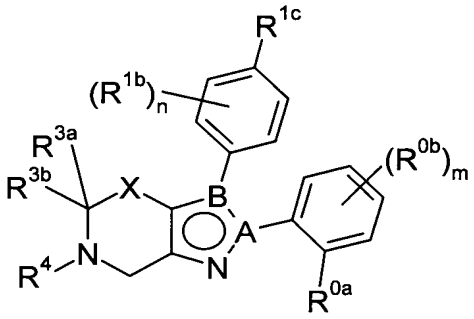


(IV)
Compounds of the present invention



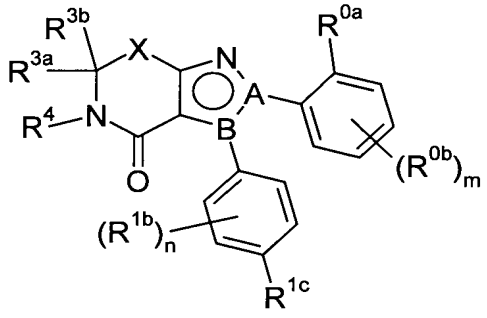
(IV)
Compounds of US 7,230,024

In all of the compounds above, X is a bond, A is nitrogen and B is carbon.

It is well known that binding to a receptor can be influenced by the orientation of the groups on the compound; consequently, one would not be able to predict with any certainty that such a compound would work until it was made and tested. Therefore, it would not be obvious that the compounds of the present invention would act as a CB-1 antagonist/inverse agonist based on the compounds disclosed and claimed in US 7,230,024.

III. Claims 1, 4, 8-11, 31, 35, 42, 43, 49, 55, 59, and 64 were rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-18 of US Patent No. 7,241,788.

Examiner erroneously states that the compounds of US Patent No. 7,241,788 are drawn to the same core. Although similar, the cores are not identical. In fact, US 7,241,788 is a divisional application of US 7,230,024 discussed above where the Examiner states that the cores are not identical but similar. Like US 7,230,024 the compounds of the present invention have a different orientation of the phenyl groups on the core as depicted below.



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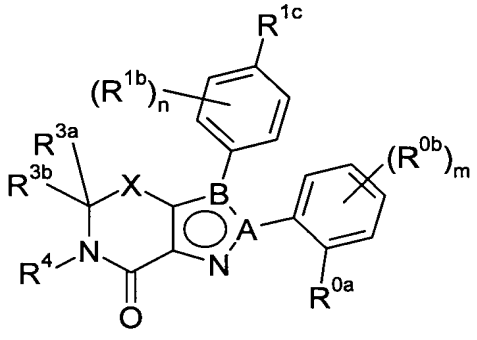

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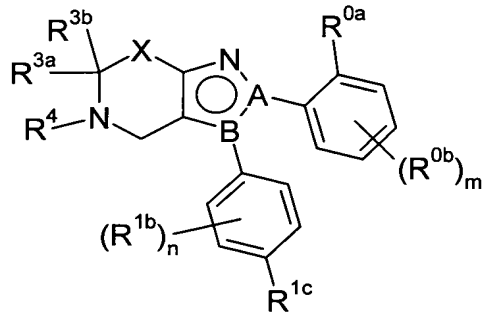
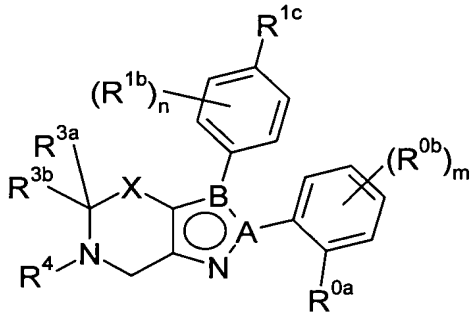


(IV)
Compounds of the present invention

X is a bond,
A is nitrogen and B is carbon



(IV)
Compounds of US 7,230,024

X is a bond,
A is carbon and B is nitrogen

Unlike, the compounds of the present invention and US 7,230,024 discussed above, the compounds of 7,241,788 are imidazole fused compounds and not pyrazole fused compounds. In fact, the present patent application was subjected to a restriction requirement based on the distinction between pyrazole (A is nitrogen and B is carbon) and imidazole (A is carbon and B is nitrogen) cores. Consequently, even the Examiner recognized that these cores are distinct and therefore could not be obvious variants. As a result, the obviousness double patenting is unfounded and should be withdrawn.

IV. Claims 1, 4, 8-11, 31, 35, 42, 43, 49, 55, 59, and 64 were rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-16 of US Patent No. 7,141,669. Unlike US 7,241,788 (e.g., 5,6-dihydro-1H-pyrrolo[3,4-d]imidazole-4-one) and US 7,230,024 (e.g., 4,5-dihydro-2H-pyrrolo[3,4-c]pyrazol-6-one) above, and the compounds of the present invention (e.g., 5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one), where the compounds comprise two five membered rings fused together, the compounds disclosed in US 7,141,669 comprise a six-membered pyrimidinone ring fused to a five-membered pyrazole ring (i.e., 2H-pyrazolo[4,3-d]pyrimidin-7(6H)-one). Unlike the compounds of the present invention, the compounds disclosed and claimed in 7,141,669 are six-membered pyrimidinone fused compounds and not five-membered dihydropyrazolone or dihydopyrazole fused compounds. In fact, the present patent application was subjected to a restriction requirement based on the distinction between a dihydropyrazolone or dihydropyrazole (X is a bond) and a tetrahydropyridinone or pyridine (X is $-C(R^{2a})(R^{2b})$) fused core. Consequently, even the Examiner recognized that cores based on a 5-membered ring fused to a 6-membered ring are distinct and therefore could not be obvious variants. As a further distinction of the cores, the compounds disclosed and claimed in US 7,141,669 would require X to be a nitrogen and bonded to the adjacent carbon with an

unsaturation. As a result, the obviousness double patenting is unfounded and should be withdrawn.

V. Claims 1, 4, 8-11, 31, 35, 42, 43, 49, 55, 59, and 64 were rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-17 of US Patent No. 7,145,012.

As discussed above for US Patent Nos. US 7,241,788 and 7,230,024, US 7,145,012 is the parent to these two divisionals. Not only do the compounds of 7,145,012 have a different orientation of the phenyl substituents as illustrated and discussed above, the compounds of 7.145,012 are based on a six-membered ring fused to a five-membered ring. By means of the restriction requirement imposed by the Examiner, she has already admitted on the record that cores based on a 5-membered ring fused to a 6-membered ring are distinct and therefore could not be obvious variants. Consequently, the obviousness double patenting is unfounded and should be withdrawn.

Applicants respectfully submit that the amended claims and the claims dependent thereon are in condition for allowance.

Respectfully Submitted:

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